

49. (Amended) A method for the treatment of stroke which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to treat stroke, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is identical to encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 134, SEQ ID NO: 5, or SEQ ID NO: 156, or an N-terminal fragment of at least 50 contiguous amino acids thereof, and wherein said method additionally includes surgery.

### REMARKS

Claims 1, 3-6, 18-23, 25-28, and 39-49 constitute the pending claims in the present application. Applicants hereby cancel, without prejudice, claims 1, 20, 21, 23, 25 and 39. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1-2. Applicants note that the amendments filed October 22, 2002 have been entered in full, and that claims 1, 3-6, 18-23, 25-28 and 39-49 are pending.

3. Applicants acknowledge that any rejection not expressly maintained has been withdrawn.

4-5. Claims 39-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

The Office Action contends that one of skill in the art cannot readily ascertain the metes and bounds of the term "bioactive fragment". Applicants disagree with this statement. The specification defines the term "bioactive fragment" (page 13, lines 9-14). Furthermore, the specification discusses bioactive fragments of hedgehog proteins in great detail, and provides exemplary bioactive fragments (page 29, line 21-page 31, line 3). Accordingly, Applicants contend that one of skill in the art can readily envision the meaning of the term "bioactive fragment" in light of the specification.

Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out the claimed fragments. Support for Applicants' amendment is found on page 29, line 21-page 31, line 3. Applicants' amendment in no way indicates acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are requested.

6. Claims 1, 3-6, 18-23, 25-28 and 31 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to enable one of skill in the art to practice the claimed invention. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

Applicants reiterate the arguments of record and contend that the claims are enabled not only for the use of polypeptides comprising a sequence identical to all or a portion of the Sonic hedgehog sequences provided in the disclosure, but also for variants of the disclosed sequences. The specification provides a detailed description of hedgehog signaling, and provides the nucleic acid and amino acid sequences of three hedgehog family members isolated from phylogenetically diverse species. Although the hedgehog family members differ in terms of their exact sequence, they share common structural and functional properties. Sonic, Desert and Indian hedgehog all bind to the receptor patched, and the teachings of Pathi et al. demonstrate that the three hedgehog family members have the same function in several different in vitro and in vivo models of hedgehog signaling. Furthermore previous experiments, published prior to the filing of the current application, have demonstrated that murine Sonic hedgehog can function in *Drosophila* despite the extensive differences in sequence identity between the *Drosophila* and mouse proteins (Chang et al. (1994)).

Additionally, the specification provides extensive teachings which would allow one of skill in the art to make and test hedgehog variants, using no more than routine experimentation, to readily select variants which retain the functions required by the pending claims. Given Applicants' disclosure and the high level of skill in the art, Applicants contend that the claims are enabled throughout their scope.

Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out certain embodiments

of the invention. Applicants' amendments in no way indicate acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

7-8. Claims 1, 21, 25-28 and 39 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by US Patent No: 5789543. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

Applicants maintain the arguments of record and contend that US Patent No. 5789543 does not sufficiently link the elements of the claimed invention, and accordingly fails to satisfy the criteria necessary to anticipate any of the pending claims. However, Applicants note with appreciation that the Examiner has indicated that Applicants' arguments regarding the obviousness of systemic administration of hedgehog proteins are persuasive, and that methods directed to systemic administration of hedgehog for the treatment of stroke and cerebral ischemia are not anticipated in light of the prior art. Accordingly, to expedite prosecution of claims directed to certain commercially relevant embodiments of the invention, Applicants have cancelled claims 1 and 39 and amended claims previously dependent upon claim 1. Cancellation of and amendment to the claims is not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

**CONCLUSION**

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

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Respectfully Submitted,



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